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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/572,644	08/25/2008	Thomas Thisted	16828.0013FPWO	4397
23552 7590 01/09/2012 MERCHANT & GOULD PC P.O. BOX 2903 MINNEAPOLIS, MN 55402-0903			EXAMINER GROSS, CHRISTOPHER M	
			ART UNIT 1636	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/572,644	Applicant(s) THISTED ET AL.	
	Examiner CHRISTOPHER M. GROSS	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 September 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 1-16, 18-20, 69-75 and 77-97 is/are pending in the application.
- 5a) Of the above claim(s) 69-75, 77-82, 85, 86, 89 and 93 is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 1-16, 18-20, 83, 84, 87, 88, 90-92 and 94-97 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>11/11/2011; 11/18/2011</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Responsive to communications entered 9/30/2011.

Claims 1-16,18-20, 69-75, 77-97 are pending.

Claims 69-75,77-82 and 85-86, 89, 93 are withdrawn.

Claims 1-16,18-20, 83,84, 87, 88, 90-92,94-97 are under consideration.

Priority

The present application was filed 8/25/2008 and is a 371 of PCT/DK2004/000630 filed 09/17/2004 and claims benefit of provisional applications 60504748 filed 09/22/2003 and 60509268 filed 10/08/2003.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Danish applications PA2003 01356 filed 09/18/2003 and PA2003 01485 filed 10/08/2003. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Withdrawn Objection(s) and/or Rejection(s)

The objection to the specification is hereby withdrawn in view of applicant's amendments thereto.

The rejection of claims 1-16,18-20, 83,84,88, 95-97 under 35 U.S.C. 102(b) as being anticipated by **Liu et al** (US Application Publication 2003/0113738) is hereby withdrawn in view of applicant's amendments to the claims.

The rejection of claims 1-16,18-20, 83,84,88, 95-97 and 87, 90, 91, 92, 94 under 35 U.S.C. 103(a) as being unpatentable over **Liu et al** (US Application Publication 2003/0113738) in view of **Pedersen** (US Application Publication 2006/012170) as

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evidenced by Barany (1991 PNAS 88:189-193) is hereby withdrawn in view of applicant's invocation of the 35 USC 103(c) shield.

The rejection of claim(s) 1-16, 18-20, 83, 84, 87, 88, 90-92, 94-97 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is hereby withdrawn in view of applicant's amendments to the claims.

New Claim Rejection(s) – 35 USC § 112

The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 18-20, 83, 84, 87, 88, 90-92, 94-97 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection concerns "new matter."

Claim 1 adds the limitation of covalently (with any type of bond at any molecular location) coupling the target oligonucleotide to the identifier oligonucleotide, however the specification as originally filed provided no implicit or explicit support for said covalent coupling with any type of covalent bond at any molecular location.

Applicants are reminded that it is their burden to show where the specification supports any amendments to the disclosure. See MPEP 714.02, paragraph 5, last sentence and also MPEP 2163.06 I.

MPEP 2163.06 notes “If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).” MPEP 2163.02 teaches that “Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes “When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not “new matter” is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure.*

Discussion

Page 28 of the 9/30/2011 contends support for the amendment may be found in claim 15 and p 70 line 16 through p 71 line 3 of the disclosure as originally filed.

The examiner notes however, original claim 15 was drawn a display molecule and identifier being joined by a cleavable linker whereas the passage on pp 70-71

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concerned covalently coupling the *ends* of oligonucleotides by phosphodiester or 3'-O-P(=O)(OH)-S-5' bonds. Critically, no mention is made of coupling a target oligonucleotide to a identifier oligonucleotide is made in either passage, much less with any covalent bond at any location.

New Claim Rejection(s) – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16,18-20, 83,84,88, 95-97 and 87, 90, 91, 92, 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Liu et al** (US Application Publication 2003/0113738) in view of **Dewhirst (WO 97/041331)**.

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The claimed subject matter is drawn to a method for identifying display molecule(s) having affinity towards molecular target(s), comprising the steps of:

providing one or more target complexes, each comprising a molecular target associated with a target oligonucleotide,

providing a library of bifunctional complexes, each bifunctional complex of the library comprising a display molecule attached to an identifier oligonucleotide that codes for said display molecule,

mixing said one or more target complexes with said library of bifunctional complexes, so that said bifunctional complexes may bind to one or more of said target complexes, by virtue of interaction between the display molecule of said bifunctional complex and the target of said target complex,

covalently coupling the target oligonucleotide of a target complex bound to a bifunctional complex, with the identifier oligonucleotide of said bifunctional complex, said coupling being in addition to the indirect coupling resulting from said binding of the display molecule to the target, and

deducing the identity of the binding display molecule(s) and/or the molecular target(s) from the coupled product between the identifier oligonucleotide(s) and the target oligonucleotide(s)

Liu et al teach, throughout the document and especially the abstract as well as paragraph 0111+, a method for synthesizing molecule libraries with a nucleic acid template.

In figure 9, Liu et al (top strand) teach providing a target complexes, each comprising a molecular target associated with a target oligonucleotide (top strand); providing a library of bifunctional complexes (bottom strand(s) with 4 or more codons), each bifunctional complex of the library comprising a display molecule attached to an identifier oligonucleotide that codes for said display molecule; mixing target complexes with said library of bifunctional complexes, so that said bifunctional complexes may

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covalently bind to one or more of said target complexes, by virtue of nucleophilic-electrophilic interaction between the display molecule of said bifunctional complex and the target of said target complex; and deducing the identity of the binding display molecule(s) and/or the molecular target(s) from the coupled product between the identifier oligonucleotide(s) and the target by gel electrophoresis, therein reading on claims 1 (in part) ,2 (codon part), 3, 6, 10, 12, 13, 88

In accordance with paragraph 0140 of Liu, the maleimide function for the reaction illustrated in figure 9 is connected through a 5' amino link structural unit incorporated during nascent oligonucleotide synthesis thus is a reaction product of two chemical entities which are not alpha amino acids nor is an alpha peptide, nor nucleic acid, and is less than 500 Dalton per claims 2, 4, 5, 7, 8, 9, 11 83, 84

Figure 9 and 45 of Liu et al includes a backbone sequences which are taken as a framing sequence per claim 14.

Unlike the oligonucleotide phosphodiester backbone, the amide bond shown in figure 9 of Liu et al is selectively cleavable by reagents such as hydroxide, reading on claim 15.

In paragraph 0177, Liu et al suggest the method may be used to write a new genetic code for preparing chelating materials which release Nickel upon photolysis, reading on claim 16.

In paragraph 0112, Liu et al envision libraries with 1,000,000 members, as set forth in claim 18.

In paragraph 0098 and figure 11A and elsewhere, Liu et al describe anticodons bearing biotin targets (i.e. of biological origin), reading on claim 19.

Figure 26 of and paragraph 0175 Liu et al discloses solid supports, reading on claim 20.

In figure 12A, Liu et al teach amplification with PCR primers, reading on claims 95, 96, 97 and 98.

Liu et al do not teach: covalently coupling the target oligonucleotide of a target complex bound to a bifunctional complex, with the identifier oligonucleotide of said bifunctional complex, said coupling being in addition to the indirect coupling resulting from said binding of the display molecule to the target of claim 1; enzymatic means to ligate the target oligonucleotide and the display oligonucleotide covalently, such as set forth in claims 87, 90, 91; a connector oligonucleotide, as set forth in claim 92; an identifier oligonucleotide with sticky ends, as set forth in claim 94.

Dewhirst teaches, throughout the document and especially the abstract and figure 5F a method for exponential nucleic acid amplification with a single primer featuring ligated hairpins which covalently connect (couple) two opposite strands of duplex DNA.

In example 1, Dewhirst teaches utilizing a restriction enzyme to generate sticky ends, reading on claim 94; a ligase to connect each strand of a DNA duplex through a hairpin, reading on claims 87, 90 and 91; and finally exponential amplification of the ligated product. Said hairpin has a complementary sticky end for the ligation to occur, which is taken as a connector of claim 92.

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to use the hairpins for single primer exponential amplification per Dewhirst et al with the library of Liu et al. In combination, the references provide covalently coupling a target oligonucleotide of a target complex bound to a bifunctional complex, with an identifier oligonucleotide of said bifunctional complex, said coupling being in addition to the indirect coupling resulting from said binding of the display molecule to the target of claim 1.

One of ordinary skill in the art would have been motivated use the hairpins for single primer amplification per Dewhirst et al for with the library of Liu et al because it would simplify deconvolution, since both the display molecule and target oligonucleotide could be decoded simultaneously in one sequencing run: In accordance with MPEP 2141 section III (A,D) citing *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. 398, 82 USPQ2d 1385,1395-6 (2007), combining prior art elements (oligonucleotide directed synthesis plus hairpin exponential amplification) according to known methods or alternatively applying a known technique (hairpin exponential amplification) to a known method (oligonucleotide directed synthesis) ready for improvement to yield predictable results are each obvious.

One of ordinary skill in the art would have had a reasonable expectation of success in applying hairpin exponential amplification per Dewhirst toward library synthesis in the manner of Liu et al because each reference concerns nucleic acid chemistry. Accordingly the teachings of Dewhirst concerning DNA hairpins appears compatible with and fall squarely in the scope of technology of interest to Liu et al.

In conclusion, the claimed invention was within the ordinary skill in the art to make and use at the time the claimed invention was made and was as a whole, *prima facie* obvious.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER M. GROSS whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571 272 0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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